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ORIGINAL ARTICLE

Safety and immunogenicity of Fc-EDA, a recombinant ectodysplasin A1 replacement protein, in human subjects

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In X-linked hypohidrotic ectodermal dysplasia, the most frequent ectodermal dysplasia, an inherited deficiency of the signalling protein ectodysplasin A1 (EDA1) impairs the development of the skin and its appendages, various eccrine glands, and dentition. The severe hypohidrosis common to X-linked hypohidrotic ectodermal dysplasia patients may lead to life-threatening hyperthermia, especially during hot weather or febrile illness. Fc-EDA, an EDA1 replacement protein known to prevent the disease in newborn animals, was tested in 2 clinical trials (human adults and neonates) and additionally administered under compassionate use to 3 infants *in utero*. The data support the safety of Fc-EDA and efficacy if applied prenatally. Anti-drug antibodies were detected after intravenous administration in adult males and nonpregnant females, but not in pregnant women when Fc-EDA was delivered intra-amniotically. Most importantly, there was no detectable immune response to the investigational drug in neonates treated by intravenous infusions and in infants who had received Fc-EDA *in utero*. In conclusion, the safety profile of this drug encourages further development of prenatal EDA1 replacement therapy.

KEYWORDS

drug safety, ectodermal dysplasia, ectodysplasin A, immunogenicity, prenatal therapy, protein replacement

1 | INTRODUCTION

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a genetic developmental disorder with a yearly incidence of approximately 4 per 100 000 live male births.¹ Many affected boys suffer severe illness in childhood with a reported mortality of nearly 30% in the first 3 years of life.² The disease is caused by a lack of the signalling protein ectodysplasin A1 (EDA1), which induces the formation of various

ectodermal derivatives during normal prenatal development.^{3,4} Disturbed EDA1 signalling results in the absence or malformation of sweat glands, sebaceous glands, teeth and hair.⁵ In patients with XLHED, a cardinal triad of hypo- or anhidrosis (reduced or absent ability to sweat), oligo- or anodontia (few and often pointed or even no teeth) and hypotrichosis (fine, sparse hair) is observed.² XLHED is associated with a highly increased risk of hyperthermia during environmental heat exposure or intense physical activity.⁶ Moreover, the lack of eccrine glands can give rise to extremely dry, eczematous skin, dry eye problems and respiratory issues such as frequent infections and allergic asthma.⁷ Individuals with XLHED may have impaired

Statement about PI: The authors confirm that the PI for this paper is Holm Schneider, MD, and that he had direct clinical responsibility for patients.

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cognitive ability and life expectancy resulting from complications of the disease. High fever and febrile seizures, for example, have the potential to cause brain injury. Common febrile infections can be life-threatening, especially in infancy. Later on, impaired temperature regulation and recurrent hyperthermic episodes may limit the child's ability to attend school and have adverse effects on the working life of adults.²

There is no approved therapy for EDA1 deficiency. Treatment options are palliative and far from adequate to address the symptoms in a clinically relevant manner. In recent years, Fc-EDA, a recombinant replacement protein made up from the receptor-binding portion of EDA1 and the Fc moiety of immunoglobulin G1, has been shown to prevent the disease in animal models.^{8–10} Based on these promising preclinical data, Fc-EDA was tested in 2 clinical trials, the main results of which are reported here. Since noninvasive prenatal diagnosis of XLHED has been established,^{11,12} treatment with Fc-EDA might be offered even prenatally, in time for inducing the formation of sweat glands and tooth germs of the permanent dentition. Fc-EDA may be injected into the amniotic fluid, which is swallowed by the foetus. It would then reach the foetal circulation via the **neonatal Fc receptor**, already expressed in the foetal intestine during the third trimester of gestation in preparation for the uptake of antibodies from breast milk right after birth.^{13,14} If delivered within the proper developmental window, a single course of treatment could be sufficient to permanently correct the most relevant clinical problems associated with XLHED. In 3 affected boys who received Fc-EDA *in utero* outside clinical studies,¹⁴ XLHED-related illness (hyperthermic episodes, respiratory problems or dry eye issues) had not developed by age 31–36 months.

The administration of a recombinant protein to patients carries a risk of eliciting anti-drug antibodies that may reduce the clinical benefit in case of repeated application by affecting clearance, pharmacodynamics and pharmacokinetics (PK) of the drug or may even neutralize its therapeutic effects entirely.¹⁵ If delivered *in utero*, anti-drug antibodies of the pregnant woman might also cause harm to the foetus, e.g. by forming immune complexes in foetal tissues. Such antibodies would limit the clinical applicability of recombinant EDA1. Therefore, the purpose of this study was to evaluate the safety and immunogenicity of Fc-EDA for the intravenous and intra-amniotic routes of administration.

2 | METHODS

2.1 | Investigational medicinal product

Fc-EDA, a recombinant fusion protein consisting of the receptor-binding portion of EDA1 and the Fc domain of human immunoglobulin G1, was produced according to Good Manufacturing Practice regulations and provided as a frozen, sterile drug product (EDI200) with a concentration of 5 mg/mL in 20mM sodium phosphate, 300mM sodium chloride, pH 7.2 and 0.02% polysorbate 20 (*w/v*) by Edimer Pharmaceuticals.

What is already known about this subject

- X-linked hypohidrotic ectodermal dysplasia (XLHED) is caused by a lack of the signalling protein ectodysplasin A1 (EDA1). Perinatal administration of Fc-EDA, a recombinant replacement protein, was shown to correct the disease phenotype in mice and dogs with XLHED.
- In the case of a pregnant woman whose foetus is to be treated, anti-drug antibodies might not only neutralize the clinical benefit of the medication but could also harm the foetus.

What this study adds

- A first-in-human study of Fc-EDA and a phase II trial in newborn infants with XLHED are reported. Additional data on safety and immunogenicity of Fc-EDA were collected in the context of prenatal compassionate use of the drug.
- Fc-EDA showed a good safety profile but proved immunogenic in XLHED-affected adults. It did not, however, elicit a specific immune response in pregnant women when injected into the amniotic fluid.
- In contrast to intravenous administration to adult subjects, neither early postnatal intravenous infusion nor prenatal intra-amniotic delivery of Fc-EDA led to the development of anti-drug antibodies in treated infants.

2.2 | Clinical trials

In a phase I safety and PK study (ClinicalTrials.gov Identifier: NCT01564225), 4 male and 2 female adult subjects with XLHED and a median age of 36 years (age range: 29–40 y) received 5 doses of undiluted Fc-EDA (3 or 10 mg/kg body weight) intravenously over 14 days (on days 0, 4, 7, 11, and 14; window of ± 24 h acceptable with a minimum of 2 days between any 2 doses). Safety assessments conducted for 6 weeks after the first dose of study drug included vital signs, laboratory evaluations (red and white blood cell counts, haemoglobin, haematocrit, differential and platelet count; serum chemistry including sodium, potassium, chloride, calcium, total protein and albumin, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase; urinalysis with dipstick and microscopy), physical examinations, 12-lead ECG, adverse event reporting, determination of PK parameters, and assessment of immunogenicity. Fc-EDA was thawed to room temperature 1 hour before administration, pooled in syringes and infused via a syringe pump system over at least 30 minutes, not to exceed an infusion rate of 10 mL/kg per hour. A protocol amendment affected the

last 2 subjects in cohort 2; doses 2–5 were infused over 120 minutes and not exceeding an infusion rate of 5 mL/kg per hour. For each of the 5 intravenous infusions, blood was collected for serum PK analysis before each dose and at 15 minutes after drug administration. Additional samples were obtained at 1, 2, 4, 8, 24, 48 and 72 hours after the first (Day 0) and final dose administration (Day 14). Blood collection for assessment of immunogenicity took place 15 and 42 days after the first dose. Each specimen was first screened by ELISA to detect the presence of any drug-specific antibodies. Positive samples then underwent a confirmatory titre test. Samples that remained positive were further tested using a validated neutralizing antibody (Nab)-specific assay. All assays were performed by Charles River Laboratories, Inc. (Mattawan, U.S.A.).

In a multicentre phase II dose-escalation study (open-label) to evaluate the safety, PK, immunogenicity and pharmacodynamics/efficacy of Fc-EDA administered to newborn infants with XLHED (ClinicalTrials.gov Identifier: NCT01775462), each subject was treated with 5 equal doses of undiluted study drug, administered intravenously over 14 days in a similar manner as in the phase I study (slow infusion with a syringe pump system into a peripheral or central vein via an intravenous catheter on days 0, 4, 7, 11 and 14; window of ± 24 hours acceptable with a minimum of 2 days between any 2 doses; infusion rate not to exceed 5 mL/kg/h). Cohorts 1 ($n = 3$), 2 ($n = 5$) and 3 ($n = 2$) received 3, 10 and 20 mg/kg, respectively, in a total volume of up to 18 mL. The study duration was 6 months, including a treatment and a safety/efficacy monitoring period, with all subjects rolling over into a long-term extension study. Safety assessments were identical to those in the phase I study described above but conducted for 6 months (regular visits at day 21 after administration and at age 2, 4 and 6 mo). Efficacy evaluations by all sites involved in the trial focused on growth and development (feeding history, body weight, length and head circumference as well as standard developmental milestone assessment using the Bayley Scales of Infant Development at age 2, 4 and 6 mo), infections and hospitalizations (captured through adverse events), primary dentition and number of secondary tooth germs (lateral jaw radiograph before treatment and at age 2 y), facial development (captured through both frontal and lateral facial photographs investigated with a special facial recognition software), sweat gland number and function (assessed by confocal laser-scanning microscopy and measurement of pilocarpine-induced sweat production as described previously),¹⁴ thermoregulation (monitoring of body temperature, heart rate and respiratory rate during exposure to ambient temperatures increasing from 33.0 to 35.0°C in a standard incubator 21 days after the first drug administration), and dry eye assessments (regular eye examinations by an experienced ophthalmologist including assessments of tear film and ocular surface, quantification of Meibomian gland ducts in the eyelids, and noninvasive measurement of tear film break-up time), as described previously.⁷

In 3 cases of male human foetuses with ultrasound-based prenatal diagnosis of XLHED^{11,12} (two monozygotic twins and a single foetus), the parents requested compassionate use of Fc-EDA *in utero* which was considered and approved by the clinical ethics committee

of the University Hospital Erlangen. Details of the procedures and very encouraging results of this prenatal application of Fc-EDA were reported previously.¹⁴ In brief, the drug (70–75 mg; same batch as administered in the phase II study) in a total volume of 14–15 mL was injected under ultrasound guidance into the amniotic cavity of each foetus at gestational week 26. Two foetuses received a second intra-amniotic injection of Fc-EDA (140 mg in 28 mL) 39 days later. Measurement of Fc-EDA concentration in the sera of pregnant women (baseline, 15 min, 3, 8 and 24 h, and 15 and 39 d after drug administration) and treated infants (7 days after the second drug administration in 2 of 3 subjects) as well as screening by ELISA for drug-specific antibodies and confirmatory titre tests were again conducted by Charles River Laboratories.

2.3 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

In the phase I study, 20 treatment-emergent adverse events (TEAEs) were recorded. Two subjects in the 10 mg/kg dose cohort experienced TEAEs determined to be probably related to study medication; 1 had chills and fatigue, the second developed phlebitis (for details see Table 1). The third subject of this cohort reported TEAEs (dizziness and headache) considered to be possibly related to the study drug (Table 1). One adverse event was severe but unrelated to study medication: Subject 1012-001 experienced a syncopal episode 6 days after the last dose (Day 20) after running up multiple flights of steps upon arriving at the study site for the follow-up visit and was in a fasting state. This syncope resolved spontaneously without treatment. The other TEAEs were mild (16) or moderate (3) in severity. No TEAE led to discontinuation of repeated dosing. All abnormalities reported for clinical laboratory parameters, electrocardiograms, physical findings, and vital signs were judged to be not clinically significant. A mild decrease in mean haemoglobin (from 14.0 to 12.6 g/dL) and haematocrit (from 42.0 to 37.2%) between days 28 and 42 occurred in 1 subject treated with the lower dose of Fc-EDA (3 mg/kg) but was not observed in any of the other subjects. Individual and mean PK parameters are presented in Table 2. The PK parameters were consistent with those obtained in prior animal studies involving intravenous dosing of Fc-EDA. Variability between subjects was considered to be small in the adult cohorts, and all values remained well below those derived from dosing at the No-observed-adverse-effect level (NOAEL). In 4 of 6 adult XLHED patients, however, repeated administration of Fc-EDA was associated with the development of anti-drug antibodies. While it provoked a striking

TABLE 1 Treatment-emergent adverse events probably or possibly related to study treatment

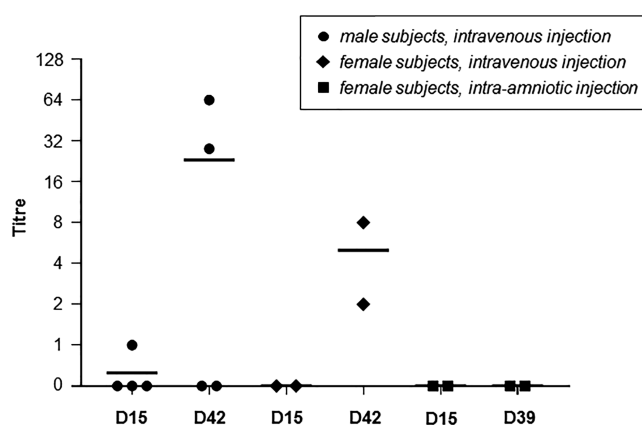
TEAE	Subject	Time of onset	Duration	Relationship to study treatment	Outcome of event
Chills and fatigue	1067-002	Day 0, 36 min after study drug infusion	<2 h	Probably related	Resolved without treatment; subsequent doses of study drug infused more slowly
Dizziness and headache	1067-001	Day 14, during study drug infusion	Until the end of study drug infusion	Possibly related	Resolved without treatment
Phlebitis at infusion site (left forearm)	1067-003	Day 11, during study drug infusion	3 d	Possibly related	Resolved after local treatment with warm compresses and administration of aspirin
Phlebitis at infusion site (right arm)	1067-003	Day 14, during study drug infusion	a few h	Probably related	Resolved after local treatment with warm compresses and administration of aspirin

TABLE 2 Pharmacokinetic parameters in adults after intravenous infusion of Fc-EDA

Cohort (dose)	Subject, sex (m/f)	Cumulative dose (mg)	AUC/dose (ng h/mL)	Cumulative AUC (ng h/mL)	C_{max} (ng/mL)	
					Dose 1	Dose 5
3 mg/kg	1012-001, m	1287	308 571	1 542 857	28 835	30 710
	1012-002, m	979.5	402 741	2 013 706	13 199	15 032
	1012-003, f	1305	274 544	1 372 721	27 277	28 057
	Mean	1191	328 619	1 643 095	23 104	24 600
	SD	183	66 408	332 041	8 613	8 391
10 mg/kg	1067-001, f	3620	1 004 683	5 023 417	105 020	108 990
	1067-002, m [†]	4645	720 574	3 602 870	128 970	83 275
	1067-003, m [†]	4455	915 960	4 579 800	109 270	88 629
	Mean	4240	880 406	4 402 029	114 420	93 631
	SD	545	145 353	726 767	12 779	13 568

AUC: area under the concentration–time curve; C_{max} : maximum plasma concentration; SD: standard deviation

[†]Dose 1 was administered over 30 minutes, whereas dose 5 was administered over 120 minutes. In both cases, PK sampling began after end of the infusion.

**FIGURE 1** Development of anti-drug antibodies following intravenous or intra-amniotic administration of Fc-EDA

humoral immune response in 2 male patients with EDA null mutations (Figure 1), no detectable anti-drug antibodies were generated in 2 male subjects with mutations compatible with low levels of endogenous EDA1 production. A weaker immune response to Fc-EDA was evident in both XLHED-affected females investigated in this study. ELISA-positive samples taken 42 days after the first dose (Day 42) were tested in a Nab-specific assay and 4/4 were found to be positive (negative cut-off value of 0.76). We observed no correlation of antibody titre with Fc-EDA dose. No clinical events were assessed to be affected by the presence of anti-drug antibodies. Serum levels of Fc-EDA at Day 42 were already too low to draw conclusions about antibody effects on PK.

Safety assessment was the primary objective of the phase II trial in neonates with XLHED. Fc-EDA was generally well tolerated, and all subjects completed the study per protocol. The 10 treated

subjects experienced a total of 166 TEAEs during the study. One TEAE (0.6%) was judged to be probably related to the study drug, and 41 TEAEs (24.7%) were considered to be possibly related. No TEAE was life-threatening or led to discontinuation of the study. Cumulatively, 156 TEAEs (94.0%) were of mild intensity, 4 (2.4%) were moderate and 6 (3.6%) severe. These 6 TEAEs, experienced by 5 subjects (50%) and considered as treatment-emergent serious adverse events, were bronchiolitis ($n = 1$), bronchopneumonia ($n = 1$), lower respiratory tract infection ($n = 1$), pyelonephritis ($n = 1$), RSV infection ($n = 1$) and upper respiratory tract infection ($n = 1$). PK analysis was performed to estimate PK parameters from serial blood draws for 10 newborn subjects. Individual and mean maximum plasma concentrations values are given in Table 3. A 3-compartment weight-normalized linear model with elimination from the central compartment, based on the modelling used in the previous phase I study, was evaluated (Table 4). Clearance was similar to that determined in adults with XLHED. All 10 treated infants, 9 of whom carried an EDA null mutation, underwent blood sampling for immunogenicity testing. No anti-drug antibodies were detected at 2 or 6 months after intravenous infusion of Fc-EDA (Table 3). Pharmacodynamic assessments, unfortunately, did not indicate improvements in perspiration, thermoregulation, primary dentition and general development. There were also no clinically significant differences between treatment groups in number and function of sweat glands or other key measures of disease response.

Prenatal intra-amniotic administration of Fc-EDA, in contrast, resulted in a rescue of sweat gland development and perspiration¹⁴ and did not lead to anti-drug antibodies in the 2 mothers of

TABLE 4 Population pharmacokinetic analysis after intravenous infusion of Fc-EDA

Parameter	Typical value
Clearance (L/d)	21.4507 • (weight/86.8)
Volume of the central compartment (L)	7.87249 • (weight/86.8)
Distribution clearance (L/d)	92.4160 • (weight/86.8)
Volume of the peripheral compartment (L)	19.7833 • (weight/86.8)
Slow distribution clearance (L/d)	13.9319 • (weight/86.8)
Volume of the deep peripheral compartment (L)	76.1963 • (weight/86.8)

the infants treated *in utero* (Figure 1). The expected absence of a foetal immune response to Fc-EDA could only be confirmed for 2 of these infants, since no blood sample was taken from the third one within 12 weeks after intra-amniotic injection of the drug.

4 | DISCUSSION

The data of both clinical trials summarized here did not indicate relevant safety issues for a short course of intravenous infusions of Fc-EDA. The phase II study in neonates with XLHED, however, also revealed the lack of efficacy in patients treated postnatally. This justified a prenatal therapeutic approach with very promising results.¹⁴

If proteins that are foreign to the body are used as therapeutic agents, the development of anti-drug antibodies may represent one of

TABLE 3 Pharmacokinetics and immunogenicity of Fc-EDA in neonates with X-linked hypohidrotic ectodermal dysplasia

Cohort (dose)	Subject, sex (m/f)	EDA mutation (hemizygous in males)	C _{max} (ng/mL)		Anti-drug antibodies	
			Dose 1	Dose 5	Month 2	Month 6
3 mg/kg	3063-001, m	Duplication of exon 3	7360	6710	Negative	Negative
	1012-001, m	p.Asn185_Pro186del	10 300	10 000	Negative	Negative
	1068-001, m	c.502+1G>A (splice-site mutation)	9080	7800	Negative	Negative
	Mean		8913	8170		
	SD		1477	1676		
10 mg/kg	3005-001, m	p.Gln247X	18 900	28 600	Negative	Negative
	3063-002, f	p.Arg156GlnfsX2	31 100	36 400	Negative	Negative
	3063-003, m	c.925-3C>G (splice-site mutation)	33 300	33 500	Negative	Negative
	3063-004, m	p.Arg155Cys	27 600	26 600	Negative	Negative
	3064-001, m	p.Arg156Cys	19 600	22 300	Negative	Negative
	Mean		26 100	29 480		
SD		6580	5583			
20 mg/kg	3064-002, m	p.Gly350Val	70 600	67 200	Negative	Negative
	1068-002, m	p.Arg156Leu	81 900	96 400	Negative	Negative
	Mean		76 250	81 800		
	SD		7990	20 648		

the biggest hurdles to overcome.¹⁵ Such antibodies may, for example, exclude identical treatment of a foetus in a subsequent pregnancy of an affected woman or could potentially cross-react with endogenous maternal EDA1. The nondetectability of anti-drug antibodies in all infants treated very soon after birth differs from what was seen in adult subjects. Immune tolerance (or ignorance) of a *nonself* protein in newborn infants, however, is not too surprising, since the innate and adaptive immune systems are not yet considered mature in early infancy.¹⁶ In addition, a population of regulatory suppressor T cells may have expanded and be capable of inhibiting the immune response.

Most interestingly, no maternal exposure was detected following intra-amniotic delivery of Fc-EDA,¹⁴ and pregnant women did not develop anti-drug antibodies, indicating the absence of relevant transplacental passage from the foetus to the mother in the first weeks of the third trimester. This finding is in agreement with previous observations of our group in XLHED mice¹⁰ and is supported by experiences with prenatal gene therapy attempts where no immune response was detected following adenoviral or AAV-mediated transfer of the clotting factor IX gene.¹⁷ Such data encourage further development of prenatal protein replacement therapy in general and pave the way to a proper clinical trial of intra-amniotic administration of Fc-EDA. Based on the safety data available so far, we conclude that the risks of this pivotal trial will mainly be attributed to the invasive procedure. Although the rate of procedure-related miscarriage is only 0.11%¹⁸ when amniocentesis is performed in the typical time window between gestational weeks 15 and 22 (but may be higher beyond that window), Fc-EDA shall not be delivered before gestational week 25. In our opinion, the prospect of greater efficacy that could be obtained through earlier treatment does not outweigh even a very low risk *quoad vitam*. Nevertheless, any preterm birth caused by prenatal drug administration would be associated with risks to baby and mother (increased neonatal morbidity and mortality, maternal infection) and may require careful reconsideration of the timing of drug delivery.

In conclusion, the safety profile of Fc-EDA both in adults and infants with XLHED justifies the decision to proceed with clinical trials involving a larger cohort of patients, even in a prenatal setting, to further evaluate EDA1 replacement therapy.

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COMPETING INTERESTS

C.D. is an employee of the Esperare Foundation, the sponsor of the planned prenatal clinical trial. K.H., N.K., and H.S. are holding patents related to the topic of this work.

CONTRIBUTORS

Conceptualization, H.S., K.H., N.K.; formal analysis, I.K., C.D., H.S.; investigation, O.D.K., I.K., P.M., F.F., D.K.G., A.C., C.B., S.M., H.S.; writing – original draft, I.K., H.S.; writing – review and editing, all authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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